

This listing of the claims replaces all prior versions in the application:

Listing of Claims:

1. (Previously Presented) A method for determining the presence of and/or a measurement for a plurality of constituents in a composite signal extending about a spectrum of interest obtained from a target sample undergoing analysis, comprising:

generating a mathematical design matrix of constituent data comprising a plurality of selected individual mathematical constituent matrix data sets, each constituent matrix data set including constituent amplitude values of a respective spectrum lineshape of a selected independent parameter over a desired number of data points of a known reference sample that is generated by a predetermined analysis method;

generating a composite mathematical matrix comprising a data set of amplitude values of a composite spectrum lineshape of the selected independent parameter over the desired number of data points for a target sample undergoing analysis that is generated by the predetermined analysis method, the composite lineshape comprising spectral contributions from a plurality of the selected individual constituents included in the design matrix;

rotating the design matrix to provide a rotated design matrix of principal components; selectively excluding data corresponding to certain of the principal components in the rotated design matrix;

generating a reduced design matrix based on the steps of rotating and excluding; and computing regression fit weighting coefficients based on data in the reduced design matrix and the composite matrix for the plurality of individual constituents to determine the levels of the selected constituents in the target sample.

2. (Original) A method according to Claim 1, wherein the computing step comprises a sequential least squares restraint in a statistical regression analysis to force the defined weighting coefficients of target constituents of interest to be positive.

3. (Previously Presented) A method for determining the presence of and/or a measurement for a plurality of constituents in a composite signal extending about a spectrum of interest obtained from a target sample undergoing analysis, comprising:

generating a mathematical design matrix of constituent data comprising a plurality of selected individual mathematical constituent matrix data sets, each constituent matrix data set including constituent amplitude values of a respective spectrum lineshape of a selected independent parameter over a desired number of data points of a known reference sample that is generated by a predetermined analysis method;

generating a composite mathematical matrix comprising a data set of amplitude values of a composite spectrum lineshape of the selected independent parameter over the desired number of data points for a target sample undergoing analysis that is generated by the predetermined analysis method, the composite lineshape comprising spectral contributions from a plurality of the selected individual constituents included in the design matrix;

rotating the design matrix to provide a rotated design matrix of principal components; selectively excluding data corresponding to certain of the principal components in the rotated design matrix;

generating a reduced design matrix based on the steps of rotating and excluding; and computing regression fit weighting coefficients based on data in the reduced design matrix and the composite matrix for the plurality of individual constituents to determine the presence of and/or measurement of the selected constituents in the target sample,

wherein the design matrix comprises at least 10 different constituent data sets, each representing a respective one of at least 10 different closely correlated chemical constituents, and wherein a plurality of the constituents have overlapping signal lineshapes in a region of the spectrum analyzed.

4. (Original) A method according to Claim 1, wherein the predetermined analysis method is NMR spectroscopy and the lineshapes correspond to intensity over a desired interval or region in a chemical shift spectrum such that intensity is the dependent parameter in the analysis.

5. (Original) A method according to Claim 1, wherein the plurality of selected individual constituents comprise lipoproteins.

6. (Previously Presented) A method for determining the presence of and/or a measurement for a plurality of constituents in a composite signal extending about a spectrum of interest obtained from a target sample undergoing analysis, comprising:

generating a mathematical design matrix of constituent data comprising a plurality of selected individual mathematical constituent matrix data sets, each constituent matrix data set including constituent amplitude values of a respective spectrum lineshape of a selected independent parameter over a desired number of data points of a known reference sample that is generated by a predetermined analysis method;

generating a composite mathematical matrix comprising a data set of amplitude values of a composite spectrum lineshape of the selected independent parameter over the desired number of data points for a target sample undergoing analysis that is generated by the predetermined analysis method, the composite lineshape comprising spectral contributions from a plurality of the selected individual constituents included in the design matrix;

rotating the design matrix to provide a rotated design matrix of principal components; selectively excluding data corresponding to certain of the principal components in the rotated design matrix;

generating a reduced design matrix based on the steps of rotating and excluding; and computing regression fit weighting coefficients based on data in the reduced design matrix and the composite matrix for the plurality of individual constituents to determine the presence of and/or measurement of the selected constituents in the target sample,

wherein the plurality of selected individual constituents comprise lipoproteins, and wherein the plurality of selected individual constituents comprise at least 35 different individual or related groupings of lipoprotein subclass constituents.

7. (Original) A method according to Claim 1, wherein the design matrix includes columns and rows of data, wherein the number of columns in the design matrix corresponds to the number of different individual constituents of interest plus at least one additional column representing spectra contributions from at least one non-relevant variable.

8. (Previously Presented) A method for determining the presence of and/or a measurement for a plurality of constituents in a composite signal extending about a spectrum

of interest obtained from a target sample undergoing analysis, comprising:

generating a mathematical design matrix of constituent data comprising a plurality of selected individual mathematical constituent matrix data sets, each constituent matrix data set including constituent amplitude values of a respective spectrum lineshape of a selected independent parameter over a desired number of data points of a known reference sample that is generated by a predetermined analysis method;

generating a composite mathematical matrix comprising a data set of amplitude values of a composite spectrum lineshape of the selected independent parameter over the desired number of data points for a target sample undergoing analysis that is generated by the predetermined analysis method, the composite lineshape comprising spectral contributions from a plurality of the selected individual constituents included in the design matrix;

rotating the design matrix to provide a rotated design matrix of principal components;
selectively excluding data corresponding to certain of the principal components in the rotated design matrix;

generating a reduced design matrix based on the steps of rotating and excluding; and
computing regression fit weighting coefficients based on data in the reduced design matrix and the composite matrix for the plurality of individual constituents to determine the presence of and/or measurement of the selected constituents in the target sample,

wherein each column of data in the design matrix corresponds to a principal component, and wherein the step of generating a reduced design matrix is carried out by using a classifier function that reviews each principal component in the rotated design matrix and accepts columns of data corresponding to the respective principal component therein based on whether the principal component has a value that is determined to improve the deconvolution.

9. (Previously Presented) A method for determining the presence of and/or a measurement for a plurality of constituents in a composite signal extending about a spectrum of interest obtained from a target sample undergoing analysis, comprising:

generating a mathematical design matrix of constituent data comprising a plurality of selected individual mathematical constituent matrix data sets, each constituent matrix data set including constituent amplitude values of a respective spectrum lineshape of a selected independent parameter over a desired number of data points of a known reference sample that

is generated by a predetermined analysis method;

generating a composite mathematical matrix comprising a data set of amplitude values of a composite spectrum lineshape of the selected independent parameter over the desired number of data points for a target sample undergoing analysis that is generated by the predetermined analysis method, the composite lineshape comprising spectral contributions from a plurality of the selected individual constituents included in the design matrix;

rotating the design matrix to provide a rotated design matrix of principal components;

selectively excluding data corresponding to certain of the principal components in the rotated design matrix;

generating a reduced design matrix based on the steps of rotating and excluding; and

computing regression fit weighting coefficients based on data in the reduced design matrix and the composite matrix for the plurality of individual constituents to determine the presence of and/or measurement of the selected constituents in the target sample,

wherein the step of generating the reduced design matrix further comprises computing a normal equations matrix from the design matrix.

10. (Original) A method according to Claim 9, wherein the design matrix comprises a number of columns " n ", a respective one each for each principal component of interest, and wherein the step of generating the reduced design matrix further comprises interrogating the normal equations matrix by applying a predetermined acceptance function to the principal components in the rotated design matrix to accept and/or reject the interrogated data to generate the reduced design matrix, the reduced design matrix having a lesser number of columns than the design matrix.

11. (Previously Presented) A method for determining the presence of and/or a measurement for a plurality of constituents in a composite signal extending about a spectrum of interest obtained from a target sample undergoing analysis, comprising:

generating a mathematical design matrix of constituent data comprising a plurality of selected individual mathematical constituent matrix data sets, each constituent matrix data set including constituent amplitude values of a respective spectrum lineshape of a selected independent parameter over a desired number of data points of a known reference sample that

is generated by a predetermined analysis method;

generating a composite mathematical matrix comprising a data set of amplitude values of a composite spectrum lineshape of the selected independent parameter over the desired number of data points for a target sample undergoing analysis that is generated by the predetermined analysis method, the composite lineshape comprising spectral contributions from a plurality of the selected individual constituents included in the design matrix;

rotating the design matrix to provide a rotated design matrix of principal components;

selectively excluding data corresponding to certain of the principal components in the rotated design matrix;

generating a reduced design matrix based on the steps of rotating and excluding; and

computing regression fit weighting coefficients based on data in the reduced design matrix and the composite matrix for the plurality of individual constituents to determine the presence of and/or measurement of the selected constituents in the target sample,

wherein the step of computing regression fit weighting coefficients is carried out with the reduced design matrix in a non-rotated state.

12. (Original) A method according to Claim 1, wherein the target sample is an *in vitro* biosample.

13. (Original) A method according to Claim 1, wherein the target sample comprises blood plasma or serum.

14. (Currently Amended) A computer program product for deconvolving the spectral contribution of a plurality of closely correlated constituents in a composite signal, the computer program product comprising:

a computer readable storage medium having computer readable program code embodied in said medium, said computer-readable program code comprising:

computer readable program code that generates a design matrix of individual selected constituent data sets for a plurality of different selected constituents in a spectrum of interest, each individual selected constituent data set including amplitude values of its associated

spectral lineshape, wherein a plurality of the different selected constituents are closely correlated with overlapping signal lineshapes in the spectrum of interest;

computer readable program code that obtains a composite signal of a target sample undergoing analysis and generates a composite matrix of amplitude values of the lineshape of the composite signal in the spectrum of interest, the target sample comprising spectra from a plurality of the selected closely correlated constituents that contribute to the composite signal;

computer readable program code for rotating the design matrix;

computer readable program code that generates a reduced design matrix; [[and]]

computer readable program code that computes regression fit weighting coefficients based on the design matrix, the reduced matrix, and the composite matrix to thereby deconvolve the spectral contribution of at least one non-target variable across the spectrum of interest in the composite signal; and

computer readable program code that determines the presence of and/or measurement of at least one constituent in the target sample based on data from at least one of: (a) the regression fit weighting coefficients; and (b) the deconvolved spectral contribution of the at least one non-target variable.

15. (Previously Presented) A computer program product according to Claim 14, further comprising computer readable program code for performing a sequential least squares analysis that evaluates the optimum weighting factors to restrain negative coefficients.

16. (Previously Presented) A computer program product according to Claim 15, wherein the computer readable program code that generates the design matrix uses "n" columns, one column for each selected individual constituent of interest.

17. (Previously Presented) A computer program product according to Claim 16, wherein the computer readable program code that generates the design matrix uses "n" columns, one column for each selected individual constituent of interest, and at least one for a parameter that contributes to the amplitude of the composite lineshape signal but is not a target constituent of interest.

18. (Currently Amended) A computer program product for deconvolving the spectral contribution of a plurality of closely correlated constituents in a composite signal, the computer program product comprising:

a computer readable storage medium having computer readable program code embodied in said medium, said computer-readable program code comprising:

computer readable program code that generates a design matrix of individual selected constituent data sets for a plurality of different selected constituents in a spectrum of interest, each individual selected constituent data set including amplitude values of its associated spectral lineshape, wherein a plurality of the different selected constituents are closely correlated with overlapping signal lineshapes in the spectrum of interest, wherein the computer program code that generates the design matrix uses "n" columns, one column for each selected individual constituent of interest and at least one for a parameter that contributes to the amplitude of the composite lineshape signal but is not a target constituent of interest;

computer readable program code that obtains a composite signal of a target sample undergoing analysis and generates a composite matrix of amplitude values of the lineshape of the composite signal in the spectrum of interest, the target sample comprising spectra from a plurality of the selected closely correlated constituents that contribute to the composite signal;

computer readable program code for rotating the design matrix;

computer readable program code that generates a reduced design matrix;

computer readable program code that computes regression fit weighting coefficients based on the design matrix, the reduced matrix, and the composite matrix to thereby deconvolve the spectral contribution of at least one non-target variable across the spectrum of interest in the composite signal; [[and]]

computer readable program code for performing a sequential least squares analysis that evaluates [[the]] optimum weighting factors to restrain negative coefficients; and

computer readable program code that determines the presence of and/or measurement of at least one constituent in the target sample based on data from at least one of: (a) the regression fit weighting coefficients; and (b) the deconvolved spectral contribution of the at least one non-target variable,

wherein the computer readable program code that generates the reduced design matrix

includes computer readable program code that interrogates the rotated design matrix and uses a predetermined classifier function to selectively include and reject data in the rotated design matrix from the reduced design matrix.

19. (Currently Amended) A computer program product for deconvolving the spectral contribution of a plurality of closely correlated constituents in a composite signal, the computer program product comprising:

a computer readable storage medium having computer readable program code embodied in said medium, said computer-readable program code comprising:

computer readable program code that generates a design matrix of individual selected constituent data sets for a plurality of different selected constituents in a spectrum of interest, each individual selected constituent data set including amplitude values of its associated spectral lineshape, wherein a plurality of the different selected constituents are closely correlated with overlapping signal lineshapes in the spectrum of interest;

computer readable program code that obtains a composite signal of a target sample undergoing analysis and generates a composite matrix of amplitude values of the lineshape of the composite signal in the spectrum of interest, the target sample comprising spectra from a plurality of the selected closely correlated constituents that contribute to the composite signal;

computer readable program code for rotating the design matrix;

computer readable program code that generates a reduced design matrix; and

computer readable program code that computes regression fit weighting coefficients based on the design matrix, the reduced matrix, and the composite matrix to thereby deconvolve the spectral contribution of at least one non-target variable across the spectrum of interest in the composite signal; [[and]]

computer readable program code for performing a sequential least squares analysis that evaluates [[the]] optimum weighting factors to restrain negative coefficients

wherein the design matrix includes columns of constituent data, each column associated with a principal component, and wherein the computer program code that generates the reduced design matrix comprises:

computer readable program code that: (a) computes a normal equations matrix from the design matrix; and (b) interrogates the normal equations matrix by applying a

predetermined classifier function to selectively include and reject data associated with certain of the principal components in the rotated design matrix from the reduced design matrix; and computer readable program code that determines the presence of and/or measurement of at least one constituent in the target sample based on data from at least one of: (a) the design matrix; and (b) the reduced design matrix.

20. (Currently Amended) A computer program product for deconvolving the spectral contribution of a plurality of closely correlated constituents in a composite signal, the computer program product comprising:

a computer readable storage medium having computer readable program code embodied in said medium, said computer-readable program code comprising:

computer readable program code that generates a design matrix of individual selected constituent data sets for a plurality of different selected constituents in a spectrum of interest, each individual selected constituent data set including amplitude values of its associated spectral lineshape, wherein a plurality of the different selected constituents are closely correlated with overlapping signal lineshapes in the spectrum of interest;

computer readable program code that obtains a composite signal of a target sample undergoing analysis and generates a composite matrix of amplitude values of the lineshape of the composite signal in the spectrum of interest, the target sample comprising spectra from a plurality of the selected closely correlated constituents that contribute to the composite signal;

computer readable program code for rotating the design matrix;

computer readable program code that generates a reduced design matrix;

computer readable program code that computes regression fit weighting coefficients based on the design matrix, the reduced matrix, and the composite matrix to thereby deconvolve the spectral contribution of at least one non-target variable across the spectrum of interest in the composite signal; [[and]]

computer readable program code that iteratively repeats a sequential least squares regression model using the design matrix, the reduced design matrix, and the composite matrix until selected target constituents of interest have been assigned non-negative weighting factors such that a sequential least squares statistical evaluation produces a non-negative solution set therefore; and

computer readable program code that outputs data regarding selected constituents in the target sample based on the deconvolved spectral contribution of the plurality of closely correlated constituents in the composite signal.

21. (Original) A computer program product according to Claim 14, wherein the composite and constituent spectral signal lineshapes are NMR spectroscopic signals.

22. (Original) A computer program product according to Claim 21, wherein the composite lineshape is obtained from a blood plasma or serum sample, and wherein the plurality of selected constituents comprise lipoprotein subclass constituents or related groupings thereof.

23. (Currently Amended) A method of deconvolving a complex signal to evaluate an *in vitro* biosample, comprising:

(a) obtaining a plurality of individual NMR spectrum reference signals of selected target constituents of interest in an *in vitro* biosample;

(b) obtaining a composite NMR spectrum signal of the *in vitro* biosample taken from a subject for analysis, the composite signal including spectral contributions from a plurality of the individual target constituents of interest;

(c) generating a design matrix of individual data sets of the amplitude of the respective reference constituents in the NMR spectrum, the design matrix having columns or rows of data that correspond to principal components that contribute to the spectral lineshape of the composite signal;

(d) rotating the design matrix;

(e) generating a reduced design matrix of principal component data by selectively excluding principal components that do not improve the estimation of the target constituents in the composite signal;

(f) deriving regression fit weighting coefficients for the selected target constituents in the composite signal;

(g) generating a calculated composite lineshape for the sample, the calculated lineshape being calculated based on the derived weighting coefficients of respective constituent reference spectrums of constituents potentially present in the sample, [[and]]

(h) determining the presence or absence of and/or the level or concentration of at least one selected constituent in the sample based on the calculated composite lineshape; and

(i) outputting data corresponding to the determined presence or absence of and/or the level or concentration of at least one selected constituent in the sample.

24. (Original) A method according to Claim 23, wherein the biosample is a blood, blood plasma, or serum sample.

25. (Original) A method according to Claim 24, wherein the constituents of interest are lipids and/or lipoproteins.

26. (Original) A method according to Claim 23, further comprising, after step (f), applying a sequential least squares analysis to restrain negative coefficients to zero until the target constituent or constituents of interest are non-negative.

27. (Original) A method according to Claim 25, wherein the reference spectra for the plurality of lipoprotein constituents includes spectra for a plurality of different lipoprotein subclasses.

28. (Original) A method according to Claim 27, further comprising the step of producing a customized subject report listing the concentrations of the lipoprotein constituents present in the sample.

29. (Original) A method according to Claim 23, further comprising obtaining an internal reference signal and aligning the reference spectra and the sample spectra based on the internal reference signal.

30. (Original) A method according to Claim 29, wherein the internal reference signal is derived from at least one NMR resonance peak produced by lactate.

31. (Original) A method according to Claim 30, wherein the internal reference signal is derived from at least one NMR resonance peak produced by glucose.

32. (Currently Amended) An apparatus for measuring lipoprotein constituents in a subject, comprising:

- an NMR spectrometer for acquiring an NMR composite spectrum of a blood plasma or serum sample; and

- a computer readable storage medium having computer readable program code embodied in the medium in communication with the NMR spectrometer, the computer-readable program code comprising:

 - computer readable program code configured to define a plurality of individual NMR constituent spectrums, each associated with a selected reference lipoprotein constituent signal lineshape, each constituent spectrum having associated spectra that contribute to the composite NMR spectrum of the blood plasma or serum sample;

 - computer readable program code configured to generate a design matrix of the selected individual constituents, the design matrix including data sets for each of the plurality of individual lipoprotein constituents in a spectrum of interest, each individual selected constituent data set including amplitude values of its associated spectral lineshape, wherein a plurality of the selected individual constituents are closely correlated with overlapping signal lineshapes in the spectrum of interest;

 - computer readable program code configured to obtain a composite signal of a target sample undergoing analysis and generates a composite matrix of amplitude values of the lineshape of the composite signal in the spectrum of interest, the target sample comprising spectra from a plurality of the selected individual constituents that contribute to the composite signal;

 - computer readable program code configured to rotate the design matrix;

 - computer readable program code configured to generate a reduced design matrix;

 - computer readable program code configured to compute regression fit weighting

coefficients based on the design matrix, the reduced matrix, and the composite matrix to deconvolve the spectral contribution of at least one non-target variable across the spectrum of interest in the composite signal;

computer readable program code configured to apply a sequential least squares analysis to the regression fit weighting coefficients to restrain negative coefficients to zero;

computer readable program code configured to determine a calculated composite lineshape based on the weighting coefficients; [[and]]

computer readable program code configured to determine the concentrations of the lipoprotein constituents in the sample undergoing analysis; and

computer readable program code configured to generate a report with the determined concentrations.

33. (Original) An apparatus for determining the presence of and/or a measurement for a plurality of constituents in a composite signal extending about a spectrum of interest obtained from a target sample undergoing analysis, comprising:

means or generating a mathematical design matrix of constituent data comprising a plurality of selected individual mathematical constituent matrix data sets, each constituent matrix data set including constituent amplitude values of a respective spectrum lineshape of a selected independent parameter over a desired number of data points of a known reference sample that is generated by a predetermined analysis method;

means for generating a composite mathematical matrix comprising a data set of amplitude values of a composite spectrum lineshape of the selected independent parameter over the desired number of data points for a target sample undergoing analysis that is generated by the predetermined analysis method, the composite lineshape comprising spectral contributions from a plurality of the selected individual constituents included in the design matrix;

means for rotating the design matrix to provide a rotated design matrix of principal components;

means for selectively excluding data corresponding to certain of the principal components in the rotated design matrix;

means for generating a reduced design matrix based on the steps of rotating and

excluding; and

means for computing regression fit weighting coefficients based on data in the reduced design matrix and the composite matrix for the plurality of individual constituents to determine the presence of and/or measurement of the selected constituents in the target sample.

34. (Previously Presented) An apparatus according to Claim 33, wherein the means for generating the reduced design matrix comprises , and wherein the means for computing employs a sequential least squares restraint in a statistical regression analysis to force the defined weighting coefficients of target constituents of interest to be positive.

35. (Previously Presented) An apparatus for determining the presence of and/or a measurement for a plurality of constituents in a composite signal extending about a spectrum of interest obtained from a target sample undergoing analysis, comprising:

means or generating a mathematical design matrix of constituent data comprising a plurality of selected individual mathematical constituent matrix data sets, each constituent matrix data set including constituent amplitude values of a respective spectrum lineshape of a selected independent parameter over a desired number of data points of a known reference sample that is generated by a predetermined analysis method;

means for generating a composite mathematical matrix comprising a data set of amplitude values of a composite spectrum lineshape of the selected independent parameter over the desired number of data points for a target sample undergoing analysis that is generated by the predetermined analysis method, the composite lineshape comprising spectral contributions from a plurality of the selected individual constituents included in the design matrix;

means for rotating the design matrix to provide a rotated design matrix of principal components;

means for selectively excluding data corresponding to certain of the principal components in the rotated design matrix;

means for generating a reduced design matrix based on the steps of rotating and excluding; and

means for computing regression fit weighting coefficients based on data in the reduced design matrix and the composite matrix for the plurality of individual constituents to determine the presence of and/or measurement of the selected constituents in the target sample,

wherein the design matrix comprises at least 10 different constituent data sets, each representing a respective one of at least 10 different closely correlated chemical constituents, and wherein a plurality of the constituents have overlapping signal lineshapes in a region of the spectrum analyzed.

36. (Previously Presented) A method according to Claim 1, wherein the selectively excluding data corresponding to certain of the principal components in the rotated design matrix comprises interrogating the rotated design matrix using a defined acceptance function to find those rotated principal components with contributions that benefit the deconvolution, then rotating back those accepted principal components to form the reduced design matrix.

37. (Previously Presented) A computer product according to Claim 14, wherein the computer readable program code that generates a reduced design matrix comprises computer program code that interrogates the rotated design matrix using a defined acceptance function to find those rotated principal components with contributions that benefit the deconvolution.

38. (Previously Presented) A method according to Claim 23, wherein step (e) generating a reduced design matrix of principal component data by selectively excluding principal components that do not improve the estimation of the target constituents in the composite signal comprises interrogating the rotated design matrix using a defined acceptance function to find those rotated principal components with contributions that benefit the deconvolution.

39. (Previously Presented) An apparatus according to Claim 32, wherein the computer readable program code configured to generate a reduced design matrix comprises computer program code that interrogates the rotated design matrix using a defined acceptance function to find those rotated principal components with contributions that benefit the deconvolution.

40. (New) A method according to Claim 1, further comprising, providing data to a clinician or user based on the determined levels of the selected constituents in the target sample data.

41. (New) A method according to Claim 3, further comprising providing data to a clinician or user based on the determined presence of and/or measurement of the selected constituents in the target sample.

42. (New) A method according to Claim 6, further comprising providing data to a clinician or user based on the determined presence of and/or measurement of the selected constituents in the target sample.

43. (New) A method according to Claim 8, further comprising providing data to a clinician or user based on the determined presence of and/or measurement of the selected constituents in the target sample.

44. (New) A method according to Claim 9, further comprising providing data to a clinician or user based on the determined presence of and/or measurement of the selected constituents in the target sample.

45. (New) A method according to Claim 11, further comprising providing data to a clinician or user based on the determined presence of and/or measurement of the selected constituents in the target sample.